The use of joint-specific and whole-body MRI in osteonecrosis: a study in patients with juvenile systemic lupus erythematosus

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Objective: This study aimed to estimate the prevalence of osteonecrosis (ON) in juvenile systemic lupus erythematosus (SLE) patients using joint-specific and whole-body MRI; to explore risk factors that are associated with the development of ON; and to evaluate prospectively patients 1 year after initial imaging.

Method: Within a 2 year period, we studied 40 juvenile SLE patients (aged 8–18 years) with a history of steroid use of more than 3 months duration. Risk factors including disease activity, corticosteroid use, vasculitis, Raynaud's phenomenon and lipid profile were evaluated. All patients underwent MRI of the hips, knees and ankles using joint-specific MRI. Whole-body STIR (short tau inversion recovery) MRI was performed in all patients with ON lesions.

Results: Osteonecrosis was identified in 7 patients (17.5 %) upon joint-specific MRI. Whole-body STIR MRI detected ON in 6 of these 7 patients. There was no significant difference between the ON and non-ON groups in the risk factors studied. One patient had pre-existing symptomatic ON. At 1 year follow-up, the ON lesions had resolved in one patient, remained stable in four and decreased in size in two. No asymptomatic patients with ON developed clinical manifestations.

Conclusion: Whole-body STIR MRI may be useful in detecting ON lesions in juvenile SLE patients but larger studies are needed to define its role.

Received 3 September 2009
Revised 12 January 2010
Accepted 14 January 2010

DOI: 10.1259/bjr/34972239

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Osteonecrosis (ON), also known as avascular necrosis, ischaemic necrosis or aseptic necrosis, is the death of bone that results in the collapse of the architectural bony structure, leading to joint pain, bone destruction and loss of function. It is a debilitating and common disorder, primarily affecting patients in the third to fifth decades of life [1]. Its prevalence is unknown, but is estimated to afflict between 10 000 and 20 000 new patients each year in the United States [2].

The final common pathway for the development of ON is ischaemia, which may be related to direct blood vessel injury (post-traumatic necrosis), altered fat metabolism and fat emboli, intravascular coagulation, elevated intracortical pressure, inhibition of angiogenesis, intramedullary haemorrhage, mechanical stress or primary cell death [3–11].

ON frequently develops in adult patients with systemic lupus erythematosus (SLE), with an estimated prevalence of 10% (range, 4–40%). The most common sites involved are the femoral head, the knee (femoral condyles and proximal tibia) and the small bones of the foot and ankle. In ON of the femoral head, the opposite hip has been found to be involved within 2 years in 55% of cases [11–13].

Only a few reports in the literature have described the assessment of ON in juvenile SLE by MRI, and these studies combined paediatric and adult patients [14, 15]. MRI appears to be a useful modality particularly in identifying pre-symptomatic ON lesions. Whole-body STIR (short tau inversion recovery) MRI permits the evaluation of the entire skeleton in a single examination that can be completed within a reasonable period of time. Bone marrow lesions, including ON, appear with high signal intensity. The ability of MRI to detect the early stages of ON may allow earlier intervention to ameliorate disease progression and to minimise more severe long-term sequelae.

We undertook a prospective study using MRI to estimate the prevalence of ON in juvenile SLE patients using joint-specific MRI, to assess the potential role of whole body STIR in detecting ON and to explore risk factors associated with the development of this disease. We also evaluated patients prospectively 1 year after initial imaging.

Methods and materials

Selection of patients

After obtaining approval from the Institutional Review Board of the Federal University of São Paulo, we followed 40 patients (aged 8–18 years) with a confirmed diagnosis of juvenile SLE (as established by the American College of Rheumatology (ACR) criteria) for

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a 2 year period [16]. All patients were treated with glucocorticoids (GC) for at least 3 months. There was no selection of patients by sex, ethnicity, corticosteroid dosage, activity or severity of the disease. One patient with previous diagnosis of ON was included.

Data collection

Demographic data describing these patients (age, sex, ethnicity, body mass index (BMI), age at onset of disease, age at first evaluation by MRI and disease duration) were collected. Information regarding GC administration before MRI, including duration of GC treatment, cumulative doses, maximum daily GC dose adjusted for weight, intravenous methylprednisolone pulsetherapy and the use of other immunosuppressive drugs, was recorded by chart review.

Clinical and laboratory evaluation

The disease activity was evaluated using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [17]. Values ≥ 4 and ≥ 8 were both evaluated. The patients were evaluated for irreversible damage using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR/DI) criteria [18]. ON was not considered in the SLICC score.

All patients with juvenile SLE underwent laboratory evaluation and the following data were recorded: total cholesterol (normal value $<170 \text{ mg dl}^{-1}$), low density lipoprotein (LDL) (normal value $<110 \text{ mg dl}^{-1}$), high density lipoprotein (HDL) (normal value $>35 \text{ mg dl}^{-1}$), very low density lipoprotein (VLDL) (normal value $<26 \text{ mg dl}^{-1}$), triglycerides (normal value $<130 \text{ mg dl}^{-1}$), IgM and IgG anticardiolipin antibodies (aCL) (values ≥ 40 for both MPL and GPL) and Venereal Disease Research Laboratory (VDRL) test (reagent or not).

Patients with positive aCL were re-evaluated 12 and 24 weeks from baseline. The cholesterol and triglycerides were measured by the colorimetric enzymatic method, aCL by solid-phase enzyme-linked immunosorbent assay (ELISA) for IgG and IgM antibodies, and the VDRL by flocculation test with non-treponemic antigen.

MRI evaluation

The imaging examinations were completed in the Diagnostic Imaging Center of the Pediatric Oncology Institute. Joint-specific MRI was obtained on a 1.5 Tesla unit (Achieva model, Philips). MRI of the hips, knees and ankles was performed on all patients, irrespective of their joint symptoms. For the hips, we used coronal T_1 weighted and T_2 weighted with fat suppression sequences together with sagittal T_1 weighted sequences. For knees and ankles, coronal T_1 weighted and T_2 weighted sequences with fat suppression were used. Whole-body STIR MRI was performed on all patients who presented with ON (whether previously or newly determined by MRI). Coronal T_1 weighted sequences were obtained with repetition times (TR) of 550–650 ms and echo times (TE) of 10–12 ms. Coronal T_2 weighted

with fat suppression sequences were obtained with a repetition time (TR) of 1900–2100 ms and a TE of 40–60 ms. Sagittal T_1 weighted sequences were obtained with a TR of 550–650 ms and a TE of 10–12 ms. Section thickness was 4 mm. The field of view was 200 mm for the hips and 180 mm for the knees and ankles. Matrix size was 256×512 for the hips and 224×512 for the knees and ankles. Total imaging time was 40–50 min. Whole-body STIR sequences were obtained with a TR of 4900–5000 ms and a TE of 60–70 ms. Section thickness was 6 mm, the field of view was 485 mm and the matrix size was 512×512 . Total imaging time was 10–15 min.

Imaging interpretation

Each imaging study was independently interpreted by two musculoskeletal radiologists (HL and WIC) who were blinded to medical record information. They interpreted the images as normal or indicative of ON.

Abnormal findings on MRI that were characteristic of ON in hips consisted of a band or ring-formed decreased signal area surrounding an area of high signal in T_1 weighted images. In epiphyseal locations, lesions with low signal intensity and epiphyseal deformities were considered to represent more advanced ischaemic marrow lesions. T_2 weighted fat-suppressed images were considered to suggest ON if they demonstrated crescentic areas of high signal intensity surrounding an area of low signal intensity in the weight-bearing portion of the femoral head, or collapse of the femoral head [19].

The extent of ON was estimated on the basis of an abnormal signal intensity in the weight-bearing portion of the femoral head as determined from a combination of coronal and sagittal MR images [19]. The index of necrotic extent ($[A/180] \times [B/180] \times 100$; where A is the necrotic arc angle in the coronal plane and B is the necrotic arc angle in the sagittal plane) was derived from the size of subchondral involvement at the midcoronal and midsagittal planes; the modified index of extent of necrosis was derived from the maximum size of subchondral involvement in both planes. The necrotic area was categorised as <40 or ≥ 40 [19] (Figure 1).

For the knees and ankles, abnormal findings on MRI that characterised ON were a geographical area of decreased signal on T_1 weighted images and increased signal on T_2 weighted images with fat suppression (Figures 2, 3, 4 and 5) [20]. For the knees, the classification of Karimova et al [20], based on the presence or absence of an osteonecrotic lesion, was used in each zone: distal femoral diaphysis, distal femoral metaphysis, medial and lateral distal femoral epiphysis, medial and lateral proximal tibial epiphysis, proximal tibial metaphysis and proximal tibial diaphysis [20]. For the ankles, the assessment was divided into five areas: distal tibial diaphysis, distal tibial metaphysis, distal tibial epiphysis, talus and calcaneum. For the knees and ankles, we recorded additional characteristics of lesions located in epiphyseal zones, including whether the lesion reached the articular surface and what proportion of this surface was involved ($<25\%$, $25\text{--}50\%$ or $>50\%$) [20].

Whole-body STIR imaging demonstrated ON lesions consisting of geographical areas of low or high signal

Figure 1. Measurement of the index of necrotic extent on (a) coronal and (b) sagittal T_1 weighted images of a femoral head. (a) The necrotic arc angle in the coronal plane. (b) The necrotic arc angle in the sagittal plane. The index of necrotic extent is 8.04 (<40).

intensity in the same locations as those highlighted by joint-specific MRI (Figures 6 and 7).

All ON patients were re-evaluated by joint-specific MRI after 1 year of follow-up by the same two radiologists. Inter- and intraobserver variability was assessed for only the first MRI. The two observers' evaluations were compared to measure their level of agreement in determining the presence and extent of ON (interobserver reliability). Intraobserver reliability was measured by comparing each observer's interpretations of a second evaluation of 20% of the patient's images with their interpretations of the first evaluation of the same images. Discrepancies in the interpretations of the two primary observers were resolved by image review by the senior observer (SK).

Statistical analysis

The ON and non-ON groups were compared by the χ^2 test or exact Fisher test for independent categorical variables and by Student's t -test for numerical variables. A p -value <0.05 was regarded as significant. The strength of agreement between the two observers was determined using the kappa coefficient. A kappa value of less than 0.4 represented a poor level of agreement; 0.41–0.60, fair agreement; 0.61–0.80, good agreement; and 0.81–1.00, excellent agreement.

Results

The patient demographic data, SLEDAI scores, SLICC scores, results of laboratory examinations and medications used are shown in Table 1. 33 patients (82.5%) were female.

The ON group comprised 7 patients (17.5%), including 6 females, with a mean age at lupus diagnosis of 12.6 years (range 8.8–16.2 years), mean age of disease duration of 2.7 years (range 0.5–5.8 years) and mean age at MRI study of 15.3 years (range 10.9–18.4 years). The non-ON group comprised 33 patients (27 female) with a mean age at lupus diagnosis of 10.9 years (range 4.0–16.6 years), a mean time of disease duration of 4.2 years (range 0.6–11.7 years) and mean age at MRI study of 15.0 years (range 8.6–18.9 years). There was no significant difference in the ages at lupus diagnosis, disease duration or ages at MRI study of those with and without ON (Table 1).

Only one of the seven patients with ON was symptomatic. This patient had an abnormal radiograph of the hip at study entry. There was no significant difference between the ON and non-ON groups in relation to SLEDAI (means 4.0 and 3.9, respectively; $p=0.96$) and SLICC score (mean 0.7 and 0.5, respectively; $p=0.51$). No ON patients had a history of peripheral vasculitis. Raynaud's phenomenon was not seen more frequently in patients with ON (Table 1).

All patients with ON had negative IgM and IgG aCL and VDRL tests. There was no significant difference in the serum total cholesterol or triglycerides levels between the groups (166.1 mg dl⁻¹ and 104.4 mg dl⁻¹, respectively, for the ON group and 170.4 mg dl⁻¹ and 102.6 mg dl⁻¹, respectively, for the non-ON group).

The seven patients with ON had lesions in the following joints: knees (six patients), hips (two patients), and ankles (three patients). There were 20 femoral, 16 tibial and 1 talar ON lesions. 3 patients (42.8%) had only 1 or 2 ON sites, whereas 4 patients (57.2%) had 5 ON sites or more (Table 2). 4 out of 14 hips (28.5%) (femoral head), 10 out of 14 knees (71.4%) (distal femur and proximal tibia) and 6 out of 14 ankles (42.8%) (distal

Figure 2. Coronal T_2 weighted fat-suppressed image of the left knee showing an osteonecrotic lesion.

tibia and talus) had ON. Asymptomatic ON was revealed in six of the seven patients with ON (85.7%) and was present bilaterally in four of these patients (57.2%) (two hips and four knees). There was no apparent difference between the groups in relation to GC therapy (duration of therapy, or maximum, cumulative or pulsetherapy doses). Statistical analysis was not performed because of the small number of patients with ON.

Whole-body STIR failed to detect ON in one patient who had a small lesion in talus that was identified by joint-specific MRI.

On the basis of the classification of Cherian et al [19], the index of extent of ON involvement of the femoral head on MRI was <40 in 3 hips and ≥ 40 in 1 hip. There was no involvement of proximal femoral metaphysis. 3 knees (2 patients) had 25–50% of involvement of the articular surface (Table 2). These patients already had involvement of metaphysis and/or diaphysis (femoral and tibial). The diaphyses (femoral and/or tibial) were involved in the remaining four patients. None of

Figure 3. Coronal T_2 weighted fat-suppressed images of the left knee showing areas of osteonecrosis (arrows). The same patient's right ankle is seen in Figure 4.

the four patients who had ankle ON had articular involvement. The sites involved were tibial diaphysis and talus.

All seven ON patients, were followed within a 1 year period. The ON lesion disappeared in one patient. This patient (patient seven in Table 2) had lesions of the distal femoral diaphysis and proximal and distal tibial diaphysis. For the remaining six patients, the MRIs showed that the lesions did not change (four patients) or had decreased in size (two patients) after this period.

The interobserver agreement presented a kappa value of 0.63 (SE=0.17; $p=0.0001$) (good agreement) for evaluation of only the presence or absence of ON in any of the joints for both the initial MRIs and those made after 1 year. The intraobserver agreement presented a kappa value of 1.00 (SE=0.38; $p=0.0041$) (excellent agreement) for the assessment of the presence or absence of ON lesions. The primary observers disagreed in only one case when evaluating the presence or absence of ON.

The mean treatment duration with GC was 2.1 years for both groups. The mean cumulative GC dose (pulsetherapy and oral GC) was 50.2 g in the ON group and 54.1 g in the non-ON group. All patients in the ON group and 31 of those in the non-ON group had been treated with methylprednisolone pulsetherapy (total doses of 30.4 g and 33.4 g, respectively). There was no significant difference between the ON and non-ON groups in relation to the maximum daily GC dose, the cumulative GC dose or methylprednisolone pulsetherapy (Table 1).

Figure 4. Coronal T_2 weighted fat-suppressed image of the right ankle showing an osteonecrotic lesion. The same patient's left knee is seen in Figure 3.

Discussion

We found a prevalence of 17.5% of ON in juvenile SLE patients. In the literature, the prevalence of ON in adult SLE patients ranges from 5% to 40% and ON was detected mainly in the first 6 months after initiation of GC therapy [21].

The most commonly affected joint in more than 25% of cases is the hip, probably because of the restricted perfusion of the femoral head [2]. ON of the knee is an established complication in paediatric haematology-oncology diseases [20], but little information is available on ON in paediatric rheumatic diseases.

The aetiology of ON in SLE patients is probably multifactorial with several risk factors having been implicated [3–7]. Sella et al [22] found that digital

Figure 5. Coronal T_2 weighted-suppressed image of the right knee showing areas of osteonecrosis (arrows).

vasculitis was a risk factor for the development of ON. Patients with history of digital vasculitis had nine times greater risk of developing ON than patients without

Figure 6. Whole-body short tau inversion recovery image showing the same osteonecrotic lesions seen in Figure 4 (arrows).

Figure 7. Whole-body short tau inversion recovery image of the patient whose right knee is shown in Figure 5 showing areas of osteonecrosis in the distal femur and proximal tibia (arrows).

previous vasculitis [22]. Mont et al [23] found a high incidence of thrombophlebitis and vasculitis in patients with ON. This suggests that the pathophysiological mechanisms of thrombotic and endothelial damage are involved in the development of ON.

Although both aCL and lupus anticoagulant are associated with risk of venous thrombosis, their role in

the pathogenesis of ON is controversial. Houssiau et al [24], in their report of a study of ON in SLE patients, stated that the prevalence of ON in SLE did not correlate with aCL; others have found a positive relationship with the presence of lupus anticoagulant [25, 26], or between ON and IgG aCL in caucasian patients [23]. In all of these studies, the patients had received GC, which is the major predisposing factor for ON. Mont et al [23] considered an aCL IgG-positive result to be of a titre ≥ 22 IU, whereas Houssiau et al [24] used ≥ 10 GPL. We considered positive values to be ≥ 40 GPL. In our study, all patients with ON were aCL negative. Since we did not know the time of development of ON in our patients, it is difficult to know if aCL was present before ON occurred. Another explanation for the negative results could be the variability of aCL levels in individual patients or the possibility that GC has played a role in decreasing antibody levels.

In relation to lipid profile and VDRL, neither of these risk factors could be correlated with the development of ON in our patients. We believe that the lack of correlation between the lipid profile and ON in our patients is due to the protective effect of hydroxychloroquine, which was used by all of the patients. Supporting the importance of disease activity as a main predictor of the development of ON in SLE, Fialho et al [27] used MRI to study 46 SLE patients over a 6 month period and found that at the end of the observation period an SLEDAI ≥ 8 was significantly more prevalent in those initially diagnosed with ON than in those without this manifestation (60% vs 19.4%) [27]. We found no correlation between disease activity and ON. Our results could be explained by the small number of ON patients: 4 out of 7 of these patients (57%) had an SLEDAI ≥ 4 . Another explanation could be that the exact time of ON onset was missed and that our assessment of disease activity was performed after the acute phase of ON. We also found no association between ON and SLICC. Because of our modest sample size and small number of patients who developed ON, our ability to determine risk factors for ON is limited. Additional studies with larger cohorts should be performed to

Table 1. Demographics, clinical and laboratory data comparing patients with and without osteonecrosis

Variables	Total (n=40)	With ON (n=7)	Without ON (n=33)	p-value
Female sex	33 (82.5%)	6 (15%)	27 (67.5%)	0.64
Age (in years) at lupus diagnosis: mean (range)	11.2 (4.0–16.6)	12.6 (8.8–16.2)	10.9 (4.0–16.6)	0.16
Disease duration (in years): mean (range)	3.9 (0.5–11.7)	2.7 (0.5–5.8)	4.2 (0.6–11.7)	0.14
Age (in years) at MRI study: mean (range)	15.1 (8.6–18.9)	15.3 (10.9–18.4)	15.0 (8.6–18.9)	0.84
Body mass index (kg m^{-2}): mean (range)	22.9 (12.5–40.3)	24.8 (17.1–34.6)	22.5 (12.5–40.3)	0.31
Raynaud's phenomenon present	17 (42.5%)	2 (5%)	15 (37.5%)	0.67
SLEDAI: mean (range)	3.9 (0.0–22.0)	4.0 (0.0–10.0)	3.9 (0.0–22.0)	0.96
SLICC score: mean (range)	0.6 (0.0–2.0)	0.7 (0.0–2.0)	0.5 (0.0–2.0)	0.51
Total cholesterol (mg dl^{-1}): mean (range)	169.7 (94.0–335.0)	166.1 (121.0–254.0)	170.4 (94.0–335.0)	0.83
Triglycerides (mg dl^{-1}): mean (range)	102.9 (39.0–426.0)	104.4 (48.0–237.0)	102.6 (39.0–426.0)	0.95
Duration of GC therapy (years): mean (range)	2.1 (0.3–7.9)	2.1 (0.3–4.8)	2.1 (0.3–7.9)	0.98
Cumulative GC dose (g): mean (range)	53.4 (4.6–206.0)	50.2 (29.1–76.5)	54.1 (4.6–206.0)	0.82
Maximum daily GC dose (mg kg^{-1} per day): mean (range)	1.1 (0.2–2.0)	1.1 (0.6–1.7)	1.2 (0.2–2.0)	0.79
Pulse GC (g): mean (range)	32.9 (0.0–162.0)	30.4 (12.0–48.0)	33.4 (0.0–162.0)	0.82

GC, glucocorticoids; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC score, Systemic Lupus International Collaborating Clinics score.

Table 2. Number of osteonecrotic sites and the classifications of Cherian et al [19] and Karimova et al [20] for the involvement of hips and knees

Patient	Gender	Age (years)	Joints involved (number of sites)	Cherian et al [19] classification	Karimova et al [20] classification
1	F	17.9	Left knee (2)		
2	M	18.2	Right knee (1)		
3	F	14.6	Left ankle (1)		
4	F	13.1	Both knees (7)		25–50% left knee
5	F	18.4	Both hips (2)		25–50% both knees
			Both knees (11)	≥40 left hip	
			Both ankles (2)	<40 right hip	
6	F	13.8	Both hips (2)	<40 both hips	
			Both knees (2)		
			Both ankles (2)		
7	F	10.9	Both knees (4)		
			Right ankle (1)		

detect potentially important risk factors and clinical differences between those who do and do not develop ON.

Despite the femoral head being the site most commonly described as being affected by ON, our results showed that the knees were more frequently involved. Four patients had involvement of the knee without hip involvement. Only four hips in two patients had ON in our study, and other joints were involved in both of these patients. GC-related ON of the knee has been reported only rarely, especially without concomitant hip involvement. Kelman et al [12] described two cases of symptomatic ON of the knee without hip involvement in young patients with a history of GC use. The discrepancy between our results and those of others results regarding ON could be explained by the underestimated prevalence of knee involvement seen in other studies that looked for ON exclusively in hips. Another explanation for this result could be the fact that the studied population is composed of children and adolescents who participate in physical activities that are more intense than those undertaken by the adult population. Such activities could predispose these patients to knee trauma and exacerbation of ON.

Karimova et al [20] defined large epiphyseal lesions as those involving more than 25% of the articular surface of the medial or lateral portion of the femoral or tibial epiphysis. In our study, three knees (two patients) had 25–50% involvement of the articular surface. Karimova et al [20, 28] emphasised the clinical importance of articular surface involvement, which has been linked to worse outcomes: progression of ON, development of arthritis and functional joint deterioration.

In the study reported by Houssiau et al [24], patients with more than six ON sites had received more GC than those with less severe disease (one or two ON sites). We did not find any association between number of ON sites and GC therapy, perhaps because of the small sample size.

In our study, the ON lesions in the distal femoral diaphysis and proximal and distal tibial diaphysis of one patient disappeared after 1 year follow-up. This indicates that, in some cases, ON lesions that are mainly on diaphysis or metaphysis can be repaired without progression.

Whole-body STIR detected ON lesions in six out of seven patients with ON. The lesions consisted of an area

of low or high signal intensity in the same location seen in joint-specific MRI. This sequence may allow us to evaluate not only the involved bones but also other sites where ON was not previously suspected.

Whole-body STIR is a reliable tool in the evaluation of bone disease. In general, hypointense tissues tend to be normal, whereas hyperintense tissues tend to be abnormal [29]. The STIR sequences are sensitive to both soft-tissue and osseous abnormalities and are highly sensitive for the detection of pathological lesions. Whole-body STIR can be used to screen the entire body in a reasonable period of time, reducing operative time and cost. It is easily applicable to the assessment of skeletal, marrow and soft-tissue disease in children and adolescents [30].

All patients with ON lesions were seen in the orthopaedic clinic. The patient with bilateral hip involvement ultimately underwent core decompression surgery on both hips. The patient with hip and knee lesions had to use crutches for walking and was encouraged to lose weight.

Conclusion

When or why ON develops in juvenile SLE is not well understood, but the results of this pilot study allow us to draw the following conclusions. First, in juvenile SLE patients, the prevalence of ON in the lower limbs is 17.5% with most patients being asymptomatic despite the involvement of multiple sites. Second, we found no association between the risk factors studied and ON, possibly because of the small sample size or the timing of imaging relative to the course of ON evolution. Third, whole-body STIR may be a promising, sensitive, practical, rapid and cost-effective tool for the detection of ON lesions. Finally, early detection of ON in juvenile SLE requires careful clinical attention: MR evaluation in high-risk patients may be appropriate as the likelihood of progression cannot yet be predicted in these patients.

Acknowledgment

This study was supported by grants from the FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo # 06/56121-7).

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